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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/076,416 | 02/19/2002 | Mechthild Rieping | 218162US0X | 2415 |
| 22850 | 7590 | 09/27/2004 | EXAMINER | |
| OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314 | | | | KERR, KATHLEEN M |
| ART UNIT | | PAPER NUMBER | | |

1652

DATE MAILED: 09/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|------------------------------------|-------------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/076,416 | RIEPING ET AL. |
| | Examiner Kathleen M Kerr | Art Unit 1652 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 20 July 2004.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 23-38 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 23-34 is/are rejected.
- 7) Claim(s) 35-38 is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>7/20/04</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-final Office action (mailed on April 20, 2004), Applicants filed a response and amendment received on July 20, 2004. Said amendment cancelled all previously pending claims 1-22 and added new claims 23-38. Thus, Claims 23-38 are pending in the instant Office action and will be examined herein.

Priority

2. A certified translation of 000613BT, which is 60/248,210, has been received. As previously noted, receipt is acknowledged of papers (DE 10116518.8) submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

3. The information disclosure statement filed on July 20, 2004 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy. Said IDS was filed to include those references previously not considered by the Examiner as noted in the previous Office action.

Withdrawn - Objections to the Specification

4. Previous objection to the specification because the title is not descriptive is withdrawn by virtue of Applicant's amendment to the title.

5. Previous objection to the Abstract for not completely describing the disclosed subject matter and for having an improper format is withdrawn by virtue of Applicant's amendment to the Abstract.

6. Previous objection to the specification for being confusing with respect to the sequence listing by not describing SEQ ID NO:4 is withdrawn by virtue of Applicant's arguments pointing out disclosure of SEQ ID NO:4 on page 8 of the specification.

7. Previous objection to the specification for being confusing containing two descriptions of the figures is withdrawn by virtue of Applicant's amendment deleting the second one on pages 25-26 should be deleted.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

8. Previous rejection of Claims 1-15 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "poxB gene or nucleotide sequence coding therefor" is withdrawn by virtue of Applicant's cancellation of said claims. Moreover, the unclear phrase does not appear in the newly pending claims.

9. Previous rejection of Claims 3-4 under 35 U.S.C. § 112, second paragraph, as being indefinite for the metes and bounds of "genes in the biosynthesis pathway" and the "metabolic pathways that reduce the formation of the L-amino acid" is withdrawn by virtue of Applicant's cancellation of said claims. Moreover, the unclear phrase does not appear in the newly pending claims.

10. Previous rejection of Claims 7-10 under 35 U.S.C. § 112, second paragraph, as being indefinite for the listing of the Markush members by numbers, “1, 2, 3...” is withdrawn by virtue of Applicant’s cancellation of said claims. Moreover, the unclear phrase does not appear in the newly pending claims.

11. Previous rejection of Claims 7-8 under 35 U.S.C. § 112, second paragraph, as being indefinite for the first “gene” in the Markush group being unclear since it is an operon is withdrawn by virtue of Applicant’s cancellation of said claims. Moreover, the unclear phrase does not appear in the newly pending claims.

12. Previous rejection of Claims 7-10 under 35 U.S.C. § 112, second paragraph, as being indefinite for being unclear as to exactly which genes must be enhanced or attenuated in the instant claims is withdrawn by virtue of Applicant’s cancellation of said claims. Moreover, the unclear phrase does not appear in the newly pending claims.

13. Previous rejection of Claims 7-8 under 35 U.S.C. § 112, second paragraph, as being indefinite for the enzyme “transhydrogenase” and the words “imparting” and “coding for” is withdrawn by virtue of Applicant’s cancellation of said claims. The enzyme transhydrogenase has been clarified in the newly pending claims; however, the words “imparting” and “coding for” have been reused in the newly pending claims. Applicant presents no arguments as to why these terms are clear. New rejections are set forth below.

14. Previous rejection of Claims 9-10 under 35 U.S.C. § 112, second paragraph, as being indefinite for the nature of the yjfA and ytfP genes is withdrawn by virtue of Applicant’s

cancellation of said claims. However, where the unclear phrase appears in the newly pending claims, a new rejection is set forth below.

15. Previous rejection of Claims 7-10 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicant's cancellation of said claims. Moreover, the unclear phrase does not appear in the newly pending claims.

16. Previous rejection of Claims 1-15 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of Applicant's cancellation of said claims. However, this same subject matter is retained in the newly pending claims. See new rejections below.

Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that Grabau *et al.*, who teach point mutations in poxB to decrease its activity, and Wang (a poxB review article) provide evidence that one of skill in the art would have been enabled at the time of the invention to attenuate poxB to the full extent of its scope. The Examiner disagrees. At the heart of this rejection is the specification's definition of attenuate, which includes sufficiently weakening unknown promoters and/or identifying alleles encoding pyruvate oxidases with lower activities would require undue experimentation as previously noted. Neither the art cited by Applicant nor the art identified by the Examiner during a search of the prior art, enables such breadth as previously noted.

17. Previous rejection of Claims 3 and 7-8 under 35 U.S.C. § 112, first paragraph, scope of enablement (enhancement vs. overexpression) is withdrawn by virtue of Applicant's cancellation of said claim. Moreover, the newly pending claims use the term "overexpression" which is well-

known in the art to not include concepts like strengthening promoters and/or using genes encoding proteins with higher activities (like the term “enhancement” was incorporating into the scope of the claim).

18. Previous rejection of Claim 6 under 35 U.S.C. § 112, first paragraph, enablement, is withdrawn by virtue of Applicant’s cancellation of said claim.

19. Previous rejection of Claims 12-15 under 35 U.S.C. § 112, first paragraph, enabling deposit, is withdrawn by virtue of Applicant’s cancellation of said claims. Moreover, the use of these deposited materials is enabled for new claims 35-38 for the following reasons:

- a) The deposit of DSM 13762 (MG442 ΔpoxB) has been perfected with the amendment to the specification to include the full address as well as the statement of irrevocability of deposit.
- b) Applicant did not comment on TOC21R and B-12288. As previously noted, these strains are deposited, and publicly available as required by FA 2511032 and US 4,391,907. If at any time during the life of any patent granted off the instant application these strains become unavailable, the validity of said patent would be in jeopardy.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

20. Previous rejection of Claims 1-11 under 35 U.S.C. § 102(e) as being anticipated by Rieping *et al.* (USPAP 2003/0059903) is withdrawn by virtue of Applicant’s cancellation of said claims. New claims drawn to the same subject matter are rejected below only wherein the translation of 60/248210 (filed November 15, 2000) does not support the claimed subject matter.

Withdrawn - Claim Rejections - 35 U.S.C. § 103

21. Previous rejection of Claims 1-11 under 35 U.S.C. § 103(a) as being unpatentable over Dunican *et al.* (USPAP 2003/0119154) in view of Kramer (J. Biotechnol. (1996) 45: 1-21) and Grabau *et al.* (1984) (see IDS) is withdrawn by virtue of Applicant's cancellation of said claims. Moreover, Applicant states for the record that Dunican *et al.* and the instant application were assigned to the same entity at the time of the invention and, thus, Dunican *et al.* cannot be used as prior art under 35 U.S.C. § 103(a).

Examiner's Comments to Applicant's Remarks Concerning Interview

22. The Examiner will comment, for the record, where she believes Applicant's representative inaccurately recounted the interview of June 1, 2004 in their remarks of July 20, 2004:

- a) On page 7, Applicant's representative comments concerning the need to overexpress yjfA and ytfP in *E. coli*; however, more accurately, it is the yjfA and ytfP genes **from *E. coli*** (able to overexpressed in any host cell) that need limitation to overcome the written description rejection.
- b) On page 7, Applicant's representative comments that the Examiner agreed to consider active regions of pyruvate oxidase as evidence for enabling its attenuation. While the Examiner does not recall such a comment, the enablement rejection is maintained in view of this evidence because the crux of the rejection is the additional embodiments of attenuation specifically recited in the specification (altering promoters, finding alleles encoding enzymes of lower activity) that are not enabled by the art, even the art cited as Wang *et al.* and Grabau *et al.* in response.

NEW ISSUES

Claim Objections

23. Claim 30 is objected to for a typographical error; the word “Corynebacteriumm” is misspelled.
24. Claims 35-38 are objected to as depending from rejected claims.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

25. Claim 30 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of the words “imparting” and “coding for” is unclear. Are the rhtB and rhtC genes meant to impart resistance? The Examiner is unfamiliar with such a functionality. As noted previously, the art describes these genes as encoding proteins that impart this functionality. If this interpretation is appropriate, amendment to the claim is required. Otherwise, clarification of how a gene imparts resistance is required. It is wholly unclear how a gene codes for export of an amino acid. Genes code for proteins, not for functions. Clarification is required.

26. Claim 34 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The phrase “an *E. coli* yjfA or ytfP” is unclear as to its metes and bounds. Firstly, must ytfP also be an *E. coli* gene? Secondly, if the claims are meant to limit to overexpressing the gene in the specification that is *E. coli* yjfA or *E. coli* ytfP, these are specific genes and should be referenced as ---the *E. coli* yjfA or the *E. coli* ytfP--- for clarity.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

27. Claim 30 is rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitations to *Corynebacterium glutamicum* pyc, *Escherichia coli* rhtB, and *Escherichia coli* rhtC are not supported by the specification as originally filed. On page 9 of the specification, these genes are mentioned with a citation. This citation is not incorporated by reference and may teach the limiting species, however, the specification as originally filed does not. Applicant is required to delete the alleged new matter or to cite clear support (page and line number) for the amendment in the specification as originally filed.

28. Claims 23-34 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for attenuating (reducing) genes by their deletion,

does not reasonably provide enablement for attenuating (reducing) genes by substituting with attenuated alleles. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To produce the products necessary to practice the claimed methods would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

On page 3, the specification describes attenuation as including using weak promoters or alleles encoding enzymes with lower activity; and in the Examples, the poxB gene is deleted

from *E. coli*. Deletion of any pyruvate oxidase gene in any *Enterobacteriaceae* is enabled since art-described means of identifying and deleting *poxB* genes are well known. However, sufficiently weakening unknown promoters and/or identifying alleles encoding pyruvate oxidases with lower activities would require undue experimentation. The specification provides no examples or guidance as to the construction of such attenuated *poxB* genes. The nature of the invention is such that while pyruvate oxidase is well known, alteration to reduce activity, particularly in allelic variant form, are not well known. One of skill in the art would be unable to predict the structure of such variants and, thus, would be unable to practice the claimed methods to the full extent of their scope.

The Examiner notes that this rejection does not apply to Claims 31 and 32, for the additional genes, because the claims require reduction and/or elimination of gene expression, which is enabled by the art.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

29. Claim 30 is rejected under 35 U.S.C. § 102(e) as being anticipated by Rieping *et al.* (USPAP 2003/0059903) effectively filed on April 13, 2001 by means of 60/283,384.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. § 102(e). This rejection under 35 U.S.C. § 102(e) might be overcome either by a showing under 37 C.F.R. § 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention “by another,” or by an appropriate showing under 37 C.F.R. § 1.131.

Rieping *et al.* teach production of amino acids, particularly threonine, valine, and lysine, using *Enterobacteriaceae* with an attenuated aceA gene in addition to an attenuated poxB gene (see Claim 12 for example). All other limitations are described in other claims and are considered disclosed by way of the combination of the claims.

Relevant References

30. The following were cited previously and are reiterated herein to complete the record:
 - a) Moriya *et al.* (USPN 6,197,559) teaches overexpression (increase) of pyruvate oxidase to make glutamate as opposed to decreasing its expression, as found in the instant claims, to make different amino acids.
 - b) Rieping (USPN 6,623,944) teaches attenuation of poxB in *E. coli* for the production of pantothenic acid; no link between pantothenic acid and amino acid production productivity is known in the art. Similarly, Dusch *et al.* (USPAP 2002/0150999) teach the same methods in Coryneform.
 - c) Bastuck (USPN 6,692,946) teaches attenuation of poxB in *E. coli* for the production of nicotinic acid; no link between nicotinic acid and amino acid production productivity is known in the art.
 - d) EP 1096013 (see IDS) was first published as CA 2322553 on April 28, 2001 and could be used as prior art against claims without priority before November 15, 2001; its disclosure is limited to the extent that Dunican *et al.* (USPAP 2003/0119154) is limited above.

Summary of Pending Issues

31. The following is a summary of the issues pending in the instant application:
- a) Claim 30 stands objected to for a typographical error.
 - b) Claims 35-38 stand objected to as depending from rejected claims.
 - c) Claim 30 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the use of the words “imparting” and “coding for”.
 - d) Claim 34 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing the phrase “an *E. coli* yjfA or ytfP”.
 - e) Claim 30 stands rejected under 35 U.S.C. § 112, first paragraph, new matter.
 - f) Claims 23-34 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for attenuating (reducing) genes by their deletion, does not reasonably provide enablement for attenuating (reducing) genes by substituting with attenuated alleles.
 - g) Claim 30 stands rejected under 35 U.S.C. § 102(e) as being anticipated by Rieping *et al.* (USPAP 2003/0059903) effectively filed on April 13, 2001 by means of 60/283,384.

Conclusion

32. Claims 23-34 are rejected and Claims 35-38 are objected to for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr
Primary Examiner
Art Unit 1652

September 23, 2004